DR. VERTER: Sure.

DR. YANCY: In the TAG column under cardiac complications 5 out of 140 patients have congestive heart failure listed as a major adverse event in Table 15.

DR. VERTER: That means that 5 subjects had at least one congestive heart failure in the first 365 days.

DR. YANCY: Okay. So when I go to Table 20, no subjects that received the device are listed as having heart failure as a major adverse event.

DR. VERTER: In the second period they are. Those occurred after day 30. They occurred between 31 days and 365 days.

DR. YANCY: Okay. Okay.

ACTING CHAIR MAISEL: Thank you. I just have one quick question. We haven't touched much on the training proposed by the sponsor for the use of the device. And I know in the packet you had proposed a training system that would allow people who had previous endovascular experience use the device after a training program with Gore. I had a question about

how you intended for physicians who may be vascular surgeons, but with no endovascular experience, how does that person say working at a community hospital, the only vascular surgeon there, how does that person become trained in the use of this device?

MR. NILSON: We feel that it is extremely appropriate for all physicians to have previous endovascular experience. We focused on those groups first. We realized that this training program is a dynamic training program and as we get into the training will be adjusted appropriately. At this point, we are working with the Agency on an appropriate path and with the physicians, consultants on how to get somebody who doesn't have the required endovascular experience access to the device.

ACTING CHAIR MAISEL: So to just summarize what you said. So a vascular surgeon or an interventional radiologist or working with a vascular surgeon, if they do not have endovascular experience, (A) they cannot get it from you and they cannot use the device indefinitely?

MR. NILSON: In parallel we are starting

programs to help disseminate endovascular experience to physicians who don't have that experience, but how we incorporate that into our training program has yet to be decided.

ACTING CHAIR MAISEL: Dr. Edmunds?

DR. EDMUNDS: Just a follow-up on Dr. Maisel's question. You should not exclude, in my opinion, thoracic surgeons who have a lot of experience with big arteries and big aortas and aneurysms and also, most importantly, vascular access. I would hope that those would not be excluded, even though they haven't put a sleeve up an aorta.

MR. NILSON: It is not our intention to exclude any particular --

DR. EDMUNDS: Well, I know, but the language does. Now, I have one question for, I think it's, Mr. Smith. Goretex is well-known for its breathe-ability if you're wearing a coat or for its porosity if you're sewing in a graft. Now, this PEF film that you put on in the modification, what does that do to the porosity of the PFTE?

MR. SMITH: The porosity and permeability

are actually two different properties of PTFE. Gore has particular expertise in manipulating the porosity and permeability, as you mentioned.

DR. EDMUNDS: Why don't you define the difference between porosity and permeability in terms of microns?

MR. SMITH: Well, I will define it in a more general way if that's okay. Permeability is a measure of what can actually pass through the wall and porosity is a measure of the void space. So if I could describe that in relation to our product, the luminal surface and abluminal surface of our product are porus and that would allow cells to penetrate so far into the material, if possible. But permeability can be reduced by inserting our layer to create the stiffness where porosity on the luminal and abluminal surface is maintained, yet permeability is reduced.

DR. EDMUNDS: Well, that answers the question, because you say you have a strip of this PEF film.

MR. SMITH: It's PTFE and FEP, both being fluoropolymers.

DR. EDMUNDS: Well, just for terminology then, let's say Goretex is Goretex, okay?

MR. SMITH: Well, Goretex --

DR. EDMUNDS: And for whatever film you want to call it --

MR. SMITH: Okay.

DR. EDMUNDS: -- is the film.

MR. SMITH: Actually, our films are a combination of PTFE, which is polytetrafluoroethylene and FEP, which is --

DR. EDMUNDS: I don't want to get into that.

MR. SMITH: Okay.

DR. EDMUNDS: What I'm trying to say is what does that film do to the native porosity of the Goretex cloth?

MR. SMITH: Could you, please, display the slide?

ACTING CHAIR MAISEL: I think in the interest of --

DR. EDMUNDS: Because that does affect healing.

MR. SMITH: I would like to point to the slide here and point out the cross-sectional SEMs of the construction of the original material and the modified material. On the bottom of each SEM would be the luminal surface. At the top portion of each SEM is the surface that incorporates our bonding tape. And you can see the dense layer. Next slide, please. You can see the dense layer. If you could reproject that slide? I'm sorry.

Again, if you look in the bottom SEM, you'll see a dense layer and I'm going to use the laser pointer. In that region is our additional PTFE/FEP film. The porosity is maintained in this region and in this region in the original device. So the original device is a three layer construction and the modified device is a four layer construction. The luminal and abluminal materials are the same and the new material is PTFE and FEP, like the original device, but with a reduction in permeability.

ACTING CHAIR MAISEL: Okay. Thank you very much. I think at this point we should move on to the questions and I'll ask Geretta to read the first

question.

DR. EDMUNDS: Well, I want to just say the conclusion of this is that you have a laminated wall of the device. I think, therefore, that you need to follow this modified device not 110 patients for five years, but I think you have to follow more than 110 patients for a lot longer, because healing and the possibility of aneurysmal dilatation or aortic dilatation brought up earlier are real threats.

ACTING CHAIR MAISEL: Thank you. Geretta?

EXEC. SEC. WOOD: If I could ask the Review Team to project the questions up on the PowerPoint? In the interest of time, the descriptions preceding these questions are quite lengthy. There are handouts available on the table if you don't have one. I would just read into the record the major portion of this question. Please, refer to these sheets for the background information.

We'll start with No. 1. Please, comment on whether the results of the clinical study with the above-mentioned safety endpoints provide a reasonable assurance of safety for the current device design in

the intended population.

ACTING CHAIR MAISEL: So without rehashing everything, I think to summarize, we can say that there does appear to be improvement in the major adverse event endpoints compared to the control group acknowledging that we have a number of major issues with the control group. What is the consensus regarding whether at the end of the day the clinical studies provide reasonable assurance without voting? Dr. Johnston?

DR. JOHNSTON: I believe they do.

DR. SOMBERG: I do, too.

DR. BRIDGES: And I.

ACTING CHAIR MAISEL: Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: After everyone is finished.

ACTING CHAIR MAISEL: Okay.

DR. FERGUSON: Are we voting?

ACTING CHAIR MAISEL: We're not voting yet. We'll vote when the vote time comes. We're just trying to get a sense of does anyone not feel that the

data provides reasonable assurance?

UNIDENTIFIED SPEAKER: I'll respond to that.

ACTING CHAIR MAISEL: Dr. Yancy?

DR. YANCY: I don't believe they do.

DR. EDMUNDS: My conclusion is that I think we should put aside the control group. It's a control for a device that they are not actually trying to market. It is for the ancestor of that device. Moreover, there are so many flaws in the heterogeneity of that group and statistical flaws where they have enough power to do propensity matching and everything else that I would much rather use as a reference what the current literature says, surgeons can do with descending thoracic aortic aneurysms.

Now, this is not a traditional comparison one, but it's a practical one. And I think that they have shown that this device has caused much fewer complications then is reported in the contemporary surgical literature. And the complications that it does -- the device does cause are relatively minor compared to the complications with this kind of

surgery and this kind of disease and usually pretty easily taken care of.

So that I think that, you know, the most serious complications occur within 14 days of the procedure. And we do have data on that. And that data is better than the contemporary treatment.

ACTING CHAIR MAISEL: Thank you. Why don't we move on to the next question, Geretta?

DR. ZUCKERMAN: Dr. Maisel, before we move on, can we just clarify one further point? There have been many comments from the cardiologists on the Panel today that we don't have the equivalent of the MAEs definition here. We have about 100 endpoints that are included in this composite. Are there any suggestions for future trials for making a more meaningful composite? Dr. Johnston or anyone else?

DR. JOHNSTON: I'm not sure I want to list the endpoints, but I think that what I was getting at in my questioning, quite apart from the minor versus major, are that within the major we need to focus on what the true differences are mostly likely going to be and obviously paraplegia, stroke, renal failure are

some of the biggies and yes, congestive heart failure is important to the patient and so on.

But in terms of coming up with endpoints for a study like this, I think we should focus on what would be expected to have the major patient impact. In this study I see paraplegia reduced. I see renal failure reduced and so on. So I regard that as very positive.

DR. LINDENFELD: Yes, I think that MI, CVA, renal failure, requiring dialysis probably. The concern I have about all of these other endpoints is that bleeding is important. But a high rate of bleeding could mask an excess stroke rate in the other group when you cumulate all the major adverse events rates. So I think it ought to be narrowed down to a real hard endpoint that would meet something, you know, a month or two months out to the patient and at least, you could look at both, but to look at a separate group of those.

Because you get all of these endpoints. They're going to mask the really critical ones, like stroke and MI and potentially even death. Although we

look at that separately.

DR. KATO: I also would like to add on, you know, as we've talked about this before at our Panel meetings, you know, some economic indicator, also as Dr. Krucoff brought up quality of life. I think, you know, those are also important.

DR. ZUCKERMAN: I think it's very important to understand our mandate. We have a big enough challenge with our Panel meetings and that's beyond our mandate. So if we could get back to the question, Dr. Lindenfeld has summarized it as really hearts, neuro and kidney is the major safety composite.

DR. LINDENFELD: With paraplegia a permanent, paraplegia would certainly be in there and a permanent neurologic defect would go along with stroke, I think.

DR. ZUCKERMAN: Okay.

DR. JOHNSTON: I'm interested in the permanent irreversible ones.

DR. LINDENFELD: Right.

DR. KRUCOFF: Just recognizing the

conundrum that if these patients are challenged to enroll and it's going to be a small denominator and these are major events or lower frequency events, that we may be as unable to figure things out if we're too restrictive to a comfort zone and it's just got to be a balance.

DR. LINDENFELD: Right.

ACTING CHAIR MAISEL: Okay. Why don't we move on. Geretta?

EXEC. SEC. WOOD: The second question. Please, comment on whether the results of the clinical studies with the above-mentioned endpoints provide reasonable assurance of effectiveness for the current device design in the intended population.

ACTING CHAIR MAISEL: The definition of effectiveness here was subjects who were free from major device-related events. Once again, we have issues with the control group, but the effectiveness of the device itself perhaps could be gleamed from some of the clinical trials. What are the thoughts of the Panel? Have we seen reasonable assurance of effectiveness? Dr. Johnston?

DR. JOHNSTON: I believe they have shown effectiveness.

DR. SOMBERG: I believe they have shown reasonable effectiveness, as well, with the understanding that it's a very difficult comparison. And since I may not be able to stay to the end, I just want to make one statement. I think what we have been discussing and troubled with this entire day is the lack of a randomized controlled trial. And I think that is really a requisite for the lead device in a given area.

ACTING CHAIR MAISEL: Does anyone feel reasonable assurance of effectiveness has not been shown?

DR. YANCY: I don't think we can dismiss the problems with design. It really disqualifies both of the first questions when we have broad definitions of what event rates are an when we have unfortunate and complex and heterogenous comparators, it is very difficult to dismiss that and then give these questions meaningful answers. So I would at least abstain from that answer and if I'm forced to say

anything, I would say no.

DR. BRIDGES: I mean, I have to say that I think that effectiveness isn't -- one of the important things is that in all the patients, there were no aneurysm ruptures and I think that that's an important -- I mean, I think that that's a take-home point. We know that if we follow these, I mean, all of our attention has been focused on comparing the stent group to the control group, but the other important comparison is comparing the stent group to the natural history of this disease.

And, you know, in that case, the fact that deployment of this device has allowed the patients to avoid the risk of aneurysm rupture, I think is something that shouldn't be overlooked.

DR. YANCY: But what if there was no risk of aneurysm rupture because the aneurysm substrate in that group was different than in the control group?

DR. BRIDGES: Well, but, I mean, you know, I think the one thing that is comparable, as has been mentioned, is the diameter of the aneurysm. I mean, it was 6.3 in one group and 6.4 in the other, and I

think we know, again, a rigorous statistical comparison, notwithstanding necessarily, because we can't say that the two groups are comparable in this particular study, but historically we know that patients with a 6.3 centimeter aneurysm have a significant risk of aneurysm rupture.

And over three years to have not a single rupture, I think, you know, clearly demonstrates within a reasonable point of view a statistically significant improvement in terms of the natural history of aneurysm rupture. Not necessarily mortality it's on, because these patients have a lot of other comorbid disease.

DR. KRUCOFF: We're on a very steep path here though, because on the one hand this could be propagated as an argument to not do randomized trials in very high risk, hard to find clinical scenarios. Just try a device and see if it looks better. And I think what a lot of us are -- what I'm wrestling with is a data set here where, frankly, the control group doesn't help me. So all we've got is a treatment group and then our sense of how different that is for

patients intuitively than doing a complex, intrinsically morbid surgical procedure.

It's hard to say that's a data-based decision. An intuitively clear decision, I think, Hank started there and I'm not sure we're going to get too much further than that. But the difference being are we really setting the stage for very high risk entities whose natural history is awful and whose current alternatives are highly morbid to say that we ought to evaluate new devices without doing randomized trials at all, just do 100 cases and see what it looks like.

DR. BRIDGES: No, I mean, let me just comment. I don't think we're saying that. I mean, I think that we don't do randomized trials in many other cases. In most of the left ventricular assist device studies, with rare exceptions, have not been randomized trials. I mean, in most of these cases it is hard to do. I mean, you could ask the question why wasn't this a randomized trial and I think that question hasn't been asked so far today. I mean, why didn't we require a randomized trial for this

comparison?

But I think that the difficulties would be that patients -- I mean, I think that's a reasonable question to ask. But I think that realistically it would be hard to do a randomized trial for this particular group of patients. And I don't think that that means that we're accepting a lower standard. I think it means that in certain cases realistically it's going to be difficult to obtain that data.

ACTING CHAIR MAISEL: Dr. Edmunds?

DR. EDMUNDS: Let me just ask the question the other way. How comfortable are you feeling denying patients this treatment? These patients are facing a lethal disease. Their choice is the lethal disease with a very bad natural history or a big operation with a lot of serious complications. Now, agreed, this is not a randomized controlled trial and surgery that's very difficult to do, but that's no excuse for not doing them.

But we're not here to define whether or not randomized trials are good. We're here to define whether or not this device should be marketed and for

what indications.

ACTING CHAIR MAISEL: Thank you. Dr. Normand?

DR. NORMAND: I was out for the first question and just so that my understanding is clear in terms of the first question, that was the one that actually used the control group. This question is on its own, correct? It's just using -- it's compared to the one arm. So that the thing about the control group, the concerns that one has to do with the control group relate to the safety endpoint, at least in terms of how we've been discussing things.

In terms of the effectiveness endpoint, that was really compared to the 80 percent. That was a one-sided test and no control group at all involved in that.

ACTING CHAIR MAISEL: Correct.

DR. NORMAND: Right?

ACTING CHAIR MAISEL: Yes.

DR. NORMAND: And I would also just like to put it on record that I don't think, for my mind, it was a problem here with regard to an observational

versus a randomized trial. That wasn't the issue. I don't have a problem with the observational study. It's the control group.

ACTING CHAIR MAISEL: Okay. Let's move on to question 3, please.

EXEC. SEC. WOOD: Please, comment on whether the difference in the prevalence of symptomatic aneurysms is clinically significant and whether this affects your comments from questions 1 and 2.

ACTING CHAIR MAISEL: Well, I think we spent three-quarters of the day today talking about the control group and the differences, not only in symptomatic aneurysms, but anatomy, New York Heart Association classification, etcetera, I think certainly has implications for our interpretation of the data. I don't know that much more can or should be said. Does anyone want to add anything?

UNIDENTIFIED SPEAKER: Well said.

ACTING CHAIR MAISEL: Okay. Question 4?

EXEC. SEC. WOOD: The proposed Indication For Use for this device is as follows: Endovascular

repair of aneurysm of the descending thoracic aorta. Please, comment on whether the Indication For Use adequately defines the patient population studied and for which the device will be marketed. Please, address the need to include the required anatomical parameters for this device in the Indications For Use statement. Note: As a point of reference, the Indications For Use of AAA approved endovascular grafts are attached as Appendix 1 to this document.

ACTING CHAIR MAISEL: I think there is no question that we need a more specific Indication For Use statement that identifies the patient populations that were in the pivotal study and the TAG 03-03 Study. It could read something like indicated for descending thoracic aortic aneurysms deemed to warrant surgical repair, fuse it for aneurysm greater than or equal to two times the diameter of the normal adjacent aorta or saccular aneurysm.

Those were the entry criteria with the following aneurysm anatomic characteristics and just list the ones that were listed in the study, aortic inner diameter 23 to 37 millimeters, lack of

significant thrombus or calcification of the proximal and distal aortic implantation sites and greater than or equal to 2 centimeter non-aneurysmal segment proximal and distal to the aneurysm. And we should include the exclusion criteria in the warning section. Dr. Kato?

DR. KATO: I think in addition to what we talked about is basically summarized on pages 38 through 44 in our packet, which also includes the inclusion and exclusion criteria that we talked about. I think it's very important that, especially for new technology, the implanters fully understand the inclusion criteria as well as the exclusion criteria that went into the data that was generated for these trials.

DR. EDMUNDS: The exclusion criteria have to include dissecting aneurysm on present evidence. I suppose it's arguable about traumatic. These are acute emergencies and it certainly should exclude mycotic aneurysm, because this is a foreign body.

ACTING CHAIR MAISEL: Well, I think the exclusion criteria would have to exclude everyone who

is excluded in the clinical trial.

DR. FERGUSON: Yes, I agree with that pretty much.

MR. MORTON: Dr. Maisel?

ACTING CHAIR MAISEL: Yes?

MR. MORTON: Could I make just a quick comment? Certainly, I respect the input of the Panel and I believe that the sponsor also is concerned about getting patient conditions very clearly defined for who should be using this. But a technical point about Indications For Use, because I knew this question was going to come up, I did a little bit of research and I think that the, if you will, rather straightforward statement about indicated for endovascular repair, etcetera, actually does meet the legal requirements for an Indication For Use.

Now, I know that the sponsor has gone further to put a warner, a warning, at least in the IFU that they are using in Europe, to go ahead and define patient conditions. And my point to the Panel is, and this may be for as much for this device as for reviews on future devices, that that does meet the

needs. A parallel that I would draw would also be with heart valves, where heart valves are usually indicated something like for replacement of a native damaged whatever, native or artificial heart valve, prosthetic heart valve. And it doesn't say anything about patient conditions need to be tolerant of anti-coagulation therapy, things like that. Those are dealt with in the warnings.

ACTING CHAIR MAISEL: I appreciate your comments. I think in this particular case, there are very specific anatomic issues that would potentially affect the safety and the effectiveness of the device. Dr. Zuckerman?

DR. ZUCKERMAN: Yes. While Mr. Morton is technically correct in that the indications should indicate the patient population and what it does, this is the reason why the Agency specifically gave you an Appendix 1, what has been the precedent for AAAs and this is also the precedent for coronary stents and we're just asking to better hone-in on indicated patient populations so we don't have misadventures. Is this appropriate?

ACTING CHAIR MAISEL: Dr. Edmunds?

DR. EDMUNDS: There is a middle ground between the ones that were in this study and the ones that you would obviously exclude, the mycotic aneurysms. For instance, a traumatic aneurysm is misnomer, but it's a rupture of the aorta from a vehicle accident or a fall usually. While this would have to be an off-label use and you would have -- if you label that in the exclusion, then it couldn't be an off-label use. But if you just don't leave it out -- if you leave it out, then it could.

ACTING CHAIR MAISEL: Your point is well-taken. I think, you know, the issue here is for us to describe what we know about the safety and effectiveness and which populations we have data on. All other populations, including the populations that were excluded from the device, we don't have data to make a comment on the safety.

DR. FERGUSON: That's right. I would feel very uncomfortable as a Panel Member, you know, recommending that we not address that. I mean, I don't want to see anything go on the labeling that we

haven't approved or disapproved as it were. And I think we haven't seen any data about ruptured aneurysms and they are planning to do that, so it will come along later. But we don't need to do that now. I don't think.

ACTING CHAIR MAISEL: Right. I would also add the comment that we do not regulate off-label use of devices nor does the FDA. Why don't we move on to the next question?

EXEC. SEC. WOOD: Based on the clinical investigation experience, please, comment on whether there are any additional warnings, precautions or contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts intended to treat thoracic aneurysms.

ACTING CHAIR MAISEL: I think we've already mentioned a number of issues, including the exclusion criteria. Are there any additional things that have not been mentioned that people would like to add to that section?

DR. NICHOLAS: In the label section,

there's nothing there about infection or mycotic aneurysms in Appendix H.

ACTING CHAIR MAISEL: Okay.

UNIDENTIFIED SPEAKER: They would be excluded now.

DR. NICHOLAS: I mean, it's pretty much given that would be the case.

ACTING CHAIR MAISEL: Any other comments? Okay.

DR. YANCY: At least two of us had concerns about the entry site and there should be some specific comments about the vascular entry site. Two of us had comments about those concerns.

ACTING CHAIR MAISEL: How would you specifically want that worded in the warnings or precautions?

DR. YANCY: I mean, that would take some time but, obviously, if you were looking at large access sites and peripheral vessels, there need to be certain provisos and precautions and things to anticipate, to prevent significant vascular trauma.

ACTING CHAIR MAISEL: Okay. Some of that

may be covered in the adverse events section or the training section. Okay.

EXEC. SEC. WOOD: Please, provide any additional comments you have on the labeling.

ACTING CHAIR MAISEL: Any other labeling comments? Mitch?

DR. KRUCOFF: Just that I think beyond training, just because on the vascular complication side at least I'm not clear whether these are complications in the aorta, i.e., from the catheter deployment site or at the access site or a mixture of both.

I think, ultimately, clarification of that enough to alert a user both through training and if there are recognizable features to any part of the anatomy that is predictive of these complications to illuminate that in the labeling, in the relative contraindications.

ACTING CHAIR MAISEL: So maybe in the table reporting adverse events, it could explicitly talk about the vascular complications and where specifically they were?

DR. KRUCOFF: Right.

ACTING CHAIR MAISEL: Dr. Zuckerman?

DR. ZUCKERMAN: Yes. I'm looking at Appendix H and there is no clinical trials section right now and there will be in any final labeling, so I would like to get some idea of what people really would like to read about in the clinical trials section. Certainly, Dr. Lindenfeld wants a very accurate indication of mortality at one and two years via tables and graphs. Are there other key features that you're looking for, Dr. Lindenfeld?

DR. LINDENFELD: No, I think that's the important data. I think just doctors, when they talk to their patients, need to know what the outcomes were of this.

ACTING CHAIR MAISEL: Along the line of patient labeling, I think the patient brochure might come under that section. I'm not sure, but the patient brochure mentioned absolutely nothing about complications from the procedure, so I think it would be worthwhile adding a section to the patient brochure talking about the risks of the procedure and spelling

them out.

MS. MOTTLE: And, Dr. Maisel?

ACTING CHAIR MAISEL: Yes.

MS. MOTTLE: That patient brochure is written at a college level, and I would like to see a table using the risks, possible adverse events on that in a very easy to read table versus all the verbiage.

ACTING CHAIR MAISEL: Excellent point. Any other comments on the labeling? Okay.

EXEC. SEC. WOOD: Please, comment on the adequacy of the proposed physician training plan as described in the Panel packet under Appendix E.

ACTING CHAIR MAISEL: I don't know if everyone has had a chance to look at that, but they have basically, as we discussed earlier, outlined a proposal for training people, physicians with endovascular experience. There is no proposal for training physicians without endovascular experience. I find that a little bit of an issue. Does anyone else share that?

DR. SOMBERG: I think that's needed and I think you're going to create two classes of

individuals and unless there is something I don't know about, I mean, maybe you may require someone to be able to put, place, aortic repair devices, abdominal aortic before you do thoracic, but that should be stated and there should be some way to access. I mean, it's common sense. People get angry if they don't feel they have any access whatsoever.

ACTING CHAIR MAISEL: So for some of the vascular surgeons here, thoracic surgeons, what sort of experience, training, what sort of training do you think would be needed for someone without any endovascular experience?

DR. FERGUSON: Well, I speak for myself, and I think for Hank, for the gray hairs of us cardiac surgeons. We have done vascular access, used to do cardiac catheterizations, but the present group are totally ignorant about it, and the idea that they have to, you know, I'm not quite sure how you're going to approach the fact.

I support the idea that the cardiothoracic surgeon or the thoracic surgeon, if you wish to call them that, who wants to get into this, and there are

going to be plenty of them because of the socioeconomics of what is going on today, there are going to be plenty that want to do this. So they should have equal and free access to the training, in my view, that everybody else has and not restricted to. It's not restricted now, as he said, is that correct?

DR. BRIDGES: It does state in that appendix that if the physician does not fit into any of the above groups, they will need to acquire the experience necessary to fit into one of the above groups. So I mean, I assume that means that -- you know, what does that mean? But my assumption would be that if you're at an institution where someone has experience, you know, you have to work with them to be able to say that you have experience and then you can be trained officially. But I mean, that's not clear, but I think that that's realistically what would happen.

ACTING CHAIR MAISEL: Dr. Johnston?

DR. JOHNSTON: I believe that the suggested training is appropriate and that for

individuals like you describe, you obtain the training yourself or, as is now being done, through programs that companies and societies cosponsor. And vascular society is, for example, now doing that as are other societies.

So I believe that with a challenging problem like this, you have to have the endovascular experience, the catheter skills, before you can actually do the Gore training. So I don't think it's their responsibility to teach the basic training. That's a society responsibility with companies, in my view.

DR. LINDENFELD: Yes. I do think one thing, it may be in here, but the study was carried out by very qualified people. It appears at least the majority had the ability to operate on these aneurysms, if appropriate, and could decide that.

And I think that it may be that this will be taken up by people who are not surgeons, so whose only choice is this procedure. And some part of this ought to just make it clear what -- it ought to be emphasized what constitutes patients for whom this is

not an adequate device. I know we have the list of the inclusions, but I think that ought to be an important part of this.

DR. FERGUSON: I think this is a bigger problem than it appears. I'm not sure this is the right place we need to work this out, but descending thoracic aortic aneurysms today are operated on by cardiothoracic surgeons not vascular surgeons that I know.

I mean, tell me if I'm wrong, but in my arena most of them are done by -- and now, the idea is is that this approach can be used by vascular surgeons and endovascular therapists and so forth. I just want to make a plea that we continue to include the thoracic surgeons where this procedure has been a part of their daily life.

ACTING CHAIR MAISEL: Dr. Johnston?

DR. JOHNSTON: Well, I don't want to say I disagree with you, but I do. Vascular surgeons, cardiothoracic surgeons as a combined group do these procedures and will do the endografts and, certainly, cardiothoracic surgeons should not be excluded. They

will have to get the catheter skills and the training.

DR. EDMUNDS: Well, we all agree, but we can get around this by just calling that an "elephant trunk" endovascular procedure.

ACTING CHAIR MAISEL: Any issues? I can't remember specifically if it was spelled out, but does the operator of the device need to have vascular surgery or cardiothoracic surgery experience or does it just need to be available?

DR. WEINBERGER: I really don't think you want to settle that today. I mean, that's really a society level. You know, there is going to be consensus societies with multiple specialties coming together to decide whether or not that should be a requirement. I think that in terms of discussing with the patient what the options are, it's prudent to have somebody who can present both options reasonably. I think that's the case.

ACTING CHAIR MAISEL: My question was more a safety issue of the use of the device at the time a device is being implanted.

DR. WEINBERGER: We don't currently

mandate that somebody be able to do an open AAA repair to do an endovascular AAA repair. So it would seem overstepping our bounds to take the further step that for a thoracic aneurysm repair, you need thoracic surgical skills.

DR. SOMBERG: It's also like coronary angiography. You don't have to be able to do coronary bypass surgery to do angioplasty, I mean, but you have to have your colleagues be ready to help you as backup.

ACTING CHAIR MAISEL: But for many years it was limited.

DR. SOMBERG: Yes, but that depends on which hospital, what institution, where you are, how that is arranged. It's not really done at advisory committee level.

ACTING CHAIR MAISEL: Okay. Why don't we move on to the final question?

EXEC. SEC. WOOD: Please, comment on the type of post-approval study or studies needed for this device and address the following considerations for each type of study: The duration of follow-up, the

outcomes of most interest, such as aneurysm-related mortality, MAEs, the upper bound with 95 percent confidence of rates that should trigger additional investigation or intervention, whether a concurrent control group should be used or whether a literature control would suffice and what surrogate measures of aneurysm-related mortality might be used if necessary.

ACTING CHAIR MAISEL: I think I will invite Dr. Normand to comment on this question, if you don't mind, the post-approval design.

DR. NORMAND: I wasn't prepared to answer some of the more clinical questions. I think there was a discussion about some of the other measures, outcomes to measure, but let me start with the bottom and work my way up.

I will start with C. I do think that it would be better to have a concurrent control, and so I think, certainly, such a control group should be used given learning, given confounding of time and given who is doing these procedures.

I'm not going to give a number for the upper bound. Are you really asking an upper bound,

what rate should trigger it or whether an upper bound should be used? What is Question C asking, whether an upper bound should be used or what the upper bound should be, because I can't answer what the upper bound should be.

ACTING CHAIR MAISEL: Perhaps the FDA could clarify that question.

DR. ZUCKERMAN: Okay. Let's take a step back. Maybe we can go back to just Appendix F. First of all, the post-approval plan as written here doesn't include that extra 100 patients that the company and Agency have been recently talking about. So what we're envisioning is, in addition to the patients being followed, there needs to be an extra n number of patients in order to set some trip wires, Dr, Normand, like one would be the mortality question at one year. And even with the sample size that we're talking about, we might only be able to detect a doubling or tripling problem for that. I mean, that's the general construct here. Does that help you out?

DR. NORMAND: I mean, it helps me out. I can't give you a number.

DR. ZUCKERMAN: Yes.

DR. NORMAND: Because I could do a private population.

DR. ZUCKERMAN: Yes. We're not looking for a number.

DR. NORMAND: Okay.

DR. ZUCKERMAN: We're looking for a useful construct where there are certain endpoints discussed today, one-year mortality.

DR. NORMAND: Yes.

DR. ZUCKERMAN: Certainly, that is going to be critical for any sample size calculation follow-up plan. We have heard Dr. Edmunds' concerns about very long-term follow-up. The plan now is for --

DR. NORMAND: Five years.

DR. ZUCKERMAN: -- five-year follow-up. It's just the major ingredients that we need to hear from the Panel.

DR. NORMAND: And I guess the major ingredient, I did read the post-market follow-up, I didn't see a concurrent control, so I guess I would recommend a concurrent control.

DR. EDMUNDS: I would add aneurysm rupture.

DR. NORMAND: Yes.

DR. EDMUNDS: Which Dr. Bridges -- and also paraplegia. This particular incident did not have an incident of paraplegia. It nevertheless is a major possibility any time you're in the descending aorta around T-12.

DR. KRUCOFF: One thing that I would suggest would be either in the time window available until this product is on the market and/or until this product has trained physicians on-site, that any attempt by the company to acquire data on patients who anatomically are good fits for this type of therapy, but who because of the timing window, again either time to approval or time until sites are trained and up and running, to gather some patients who are really well-characterized in the modern era, characterized anatomically who are candidates for this device, but who are treated surgically, would be, in my opinion, a very useful not quite randomized, but at least filling some important gaps about really the potential

benefit of this device relative to other options in a little more comparable, completely comparable patient population.

DR. NORMAND: Yes, and so I will just echo that. When I was saying a concurrent control, I'm talking about one that would be a concurrent control in terms of --

DR. KRUCOFF: No, I'm totally with you, Sharon.

DR. NORMAND: Yes.

DR. YANCY: Just a point of clarification on that issue though. If the technology is approved and has an FDA indication, I would think that most post-market instruments would be at most surveys or registries. And if there is a concurrent control, which I believe is intellectually and appropriately necessary, practically speaking it would seem to be only those who decline the intervention, because if there is an indication for it, I wonder how you can, in a priori fashion, determine a control group other than patients' preference.

DR. KRUCOFF: I was actually trying to

suggest a window of convenience that would not deprive patients of therapy nor necessarily slow down the company's objectives. But the window of time, you know, right now you have got a network of sites who know this device very well and if, I'm assuming, there is not continued access, that may be a wrong assumption, but if there is a window of time before the device is approved and on the market, you already have a network of sites who know what these patients look like.

If you have plans to start training sites, those sites are not going to be up and running until they are trained, and so there is probably an aggregate here of somewhere around six months, nine months, I don't know, but a time when you could actually identify patients who can't wait six, nine months who will be operated on, but who actually fit concurrently a little more the population who is going to be treated.

ACTING CHAIR MAISEL: Yes. My understanding is the device does remain available to the investigator sites through the IDE. I think the

reality of doing a concurrent control the way we would like is difficult and maybe, at the very least, the appropriate -- you know, all the things we wanted to see today that we didn't get to see related to the anatomy and neck length and all of those things could be collected.

DR. LINDENFELD: I think it would be nice to see a few more patients that are outlined in this appendix. It's 250 of which, if I understand it correctly, 140 are the original device. We now have a modified device, so that's only 110 of that and 25 percent of those are dead at one year. So when you look at the mortality, it's not going to be very many patients who are going to be out to five years and it's only going to be 110 to start out with the new device, so I think that needs to be beefed up a bit.

ACTING CHAIR MAISEL: So I think, certainly, another study of real-world use of non-study patients is necessary as was proposed. The precise number of patients, I think, would depend on the power calculations based on the endpoints that were ultimately decided upon, including mortality, the

paraplegia, aneurysm rupture, etcetera. Is that enough for you, Bram?

DR. ZUCKERMAN: Yes. Two other questions. One is there is a three-tiered physician training program. Should there be a representative number of cases from each tier to show that this technology is diffusible, A. And B is in order to improve the quality of this suggested post-approval study, should the CEC and the core lab continue to operate and be a part of this?

ACTING CHAIR MAISEL: As far as the training goes, I think, certainly, the experience of the operator would be very valuable information to see what the learning curve looks like and how many cases should be performed. Mitch?

DR. KRUCOFF: I would like to encourage the company, in fact, that not only would gathering, continuing to gather objectively core lab quantified data, be potentially a better way to educate operators. You guys indicated that 03-03, you had less vascular problems, less bleeding. That is actually why the curves, the event rates separate and

that somewhere in there you have learned something.

You guys have learned something, that the more you can quantify that and build it into your training, that is also a challenge to your engineers. That is also a path to make the device a little more flexible or to think about engineering the device to avoid those kinds of vascular complication situations.

So I would encourage the company to think about your own benefit, as well as patients, in your training to continue to quantify the angiographic anatomy and understand what is predictive about a greater likelihood of the device having a problem, and either select that out in your training and/or use that to stimulate your own engineering directions.

ACTING CHAIR MAISEL: Question 9 you can read, but I think we have already answered it.

EXEC. SEC. WOOD: I think so, too. In light of the discussion regarding Panel Question 8, please, comment on the adequacy of the proposed post-approval study plan as described in the Panel package.

ACTING CHAIR MAISEL: I think we have already answered that question. So are there any

final comments from the Panel before we move on? At this point, I would like to open the public hearing session of this meeting and ask if there is anyone who would like to address the Panel.

DR. KARMY-JONES: All right. Well, I will try and be quick again. Just to introduce myself, my name is Riyad Karmy-Jones and I am a cardiothoracic surgeon from Seattle, and I had five points, a lot of them that you were all mentioning, but it's something we talk about every day when we see an individual patient. And I'm talking from the perspective as a thoracic surgeon and an interventional radiologist who feels very acutely and in real-time the need for an appropriate thoracic endograft device.

The first comment is the neck, and this has been discussed, some of the anatomical differences between the control groups, and I would like to, in a rather simplistic way, just point out that if you have a 2 centimeter neck or a 1 centimeter neck, operatively that doesn't make a difference. It's not a prognostic difference.

There obviously are some differences if

you have to clamp proximal and subclavian, vagus nerve, how calcified is the vessel, but in all practical intents and purposes is that the bulk of these patients were excluded simply on the basis of the 2 centimeter neck, that from that perspective, from what I can tell, the control groups were clinically similar.

The second is a comment about access. You know, if you do a left heart bypass or a full bypass using the femoral artery for an extensive thoracic aortic aneurysm, you use 18 or a 20 millimeter cannula, a 20 French cannula, a cannula, and these are fairly large cannula and they are about the same size as the introducer devices that you use not only for thoracic endograft devices, but also for infrarenal aortic devices.

And the same clinical judgment is required to put someone on bypass as it is to put a sheath on. You still have to be aware of tortuosity, calcified plaque, risk of dissection, bleeding and so on and so forth, and sometimes vessels require a conduit and sometimes you have to go retroperitoneal iliac and you

take it into account, but these are all.

Assuming that by going to surgery and not using a sheath you can avoid some of the vascular complications isn't totally accurate, but we have to assess all these on an individual basis.

Training, I will be brief. All the societies are now trying to come up with the training guidelines. We have gone to the extreme in terms of endovascular training, that all of us who do endovascular now are trained fully in interventional radiology. When we approach a thoracic patient, as we do in any endovascular device, there has to be someone who can do the open operation, someone who can do the endovascular and someone who can do the interventional work, and sometimes that's one person. But that is where all the societies are trying to get together and go to, and that's coming along.

And my last few points are when you talk about complication rates, when I talk to a person, an elderly woman who has, just referred in the lunch break, a procedure, you know, I talk to her about a 50 percent complication rate and most patients are

willing to accept the risk of death when they know that they have a 7 centimeter aneurysm and they may be or may be not symptomatic.

But one of the issues you have to talk to them about is quality of life. These patients are largely dying not from the aneurysm once they have been treated, but from comorbidities, which can be accelerated, obviously, with an operative repair. Patients are dying of heart attack and so on.

But to look at that person and say, you know, you can have two years with good quality of life before you drop dead of a heart attack, we don't couch it quite like that, or you can have two years paralyzed and in renal failure with bed sores before you die, which are some of the consequences of the operative approach, that for me is a clinically important difference and above and beyond simple mortality statistics and a huge difference.

ACTING CHAIR MAISEL: Yes. If you could wrap it up in the next 30 seconds, please.

DR. KARMY-JONES: Yes. The last thing, I'm not sure how you're going to be able to randomize

this, do something like this in a randomized fashion. I'm not aware that the AAA devices were randomized. I don't think patients would accept it, and I would be scared to turn a patient down who is a good endograft candidate for an open operation. Thank you.

ACTING CHAIR MAISEL: Any other individuals who would like to address the Panel? Yes, sir?

DR. SICARD: Yes. I'm Greg Sicard. I'm a vascular surgeon in Saint Louis and I am President of the Society for Vascular Surgery. Again, this is the first experience I have had through a full Panel and I really appreciate this experience. I think it's eye opening.

I was in Argentina in October of 1990 when Juan Perotti showed me the first two cases that he had performed with endoluminal treatment of an abdominal aortic aneurysm in very high risk patients and I realized, at that point, that this was going to work.

I saw through the '90s how trials were performed, and I recall vascular surgeons that were interested in this technology, that as we would meet

with industry to give opinions about how these devices should be constructed, that one of the common questions was we need a thoracic device, because it was evident that in that sector, that anatomical sector, this technology could make a big difference.

And I think today we have seen what the difference that this technology can make. And I think somebody in the Panel asked a question that I think is very appropriate. Are we ready to deny this to patients that can benefit based on all the information that was shown here?

I understand the concerns about the controls. I understand that Level I randomized trial offers the best science, but I really don't know of any vascular or cardiovascular surgeon that is embracing this technology that would ethically randomize a patient between open surgery and endoluminal devices if they had it available going forward.

So I thank you for the opportunity to comment and I really encourage you to embrace this technology, because its impact is going to be much

more significant than infrarenal aortic aneurysm endografting where it has made a significant impact. Thank you.

ACTING CHAIR MAISEL: Thank you. Yes, sir? Please, keep your comments to about two minutes, please.

DR. WHITE: Yes. My name is Rod White. Again, I am Secretary of SVS. I would like to address two points. One is that this is probably the fifth Panel that I have attended related to endoluminal graft technologies and, in the earlier evaluations, randomization was considered. In our own case where we have been dealing with this now with the IRB at our institution, the issue has been considered and the early attempts were to do this in these groups of patients.

The IRB itself has decided this is unethical, that you cannot offer a patient -- this is so clear in the minds of the IRBs that are familiar with doing this, that randomization is not a consideration. Again, it would be an unethical consideration and they would not look at a protocol.

The other is I would only reinforce what Dr. Sicard said, and I am sympathetic as someone who has been involved in implants for more than 20 years, been on the NIH panels, evaluated things and insisted on the highest level of science, that in this regard where we're confounded with a lot of variables, it is absolutely clear to clinicians and patients who look at this technology that it's a hands down in favor of the patients for the group that has been studied.

I understand everybody's concern and I think they are appropriate, but if you have treated these patients and you deal with them day to day, this is absolutely a technology that is of benefit to the patients with the data set we have. Thank you.

ACTING CHAIR MAISEL: Thank you. Any other people? Anyone else who wants to speak should come up to the podium now. Otherwise, this will be the last speaker. Thank you.

DR. TUCHEK: An envious position. I'm Dr. Tuchek from Loyola University Medical Center. I'm a cardiac surgeon there. A couple of comments. In principle, I agree with the sponsor that these two

groups are fairly similar. They are all sick, old patients with thoracic aneurysms. I don't think we want to forget that. Are they exactly alike? Of course not. No group ever is even in the randomized trial.

But if I lined up my last 10 cases of thoracic stent grafts at Loyola, I would be hard pressed to find too many differences in those patients fundamentally. They are all old, hypertensive vasculopaths that need a thoracic stent graft or an open operation. I don't think they are that dissimilar.

Regarding randomized trials, correct me if I'm wrong, but I think all four currently approved abdominal stent grafts were approved without a randomized trial. They are difficult, they are long and they are costly, and I think in this particular sick patient population, I think a randomized trial simply isn't feasible.

Regarding some of the issues about the TAG device, issues about vascular complications, for example, being high, yet the paraplegic rate is low.

To condemn that technology over issues like vascular complications without considering what I feel is the far more important advantages like a decreased amount of paraplegia would be missing the forest for the trees and I simply don't want the Panel to sort of forget the bigger picture.

Patients are currently dying in the operating room or getting paralyzed from an open operation that I do fairly well or they are dying at home, because they are afraid to be paralyzed. They would rather die than have no ability to walk.

And I think when we have at our fingertips a device platform that, no matter how you slice it, no pun intended, no matter how you slice it is clearly a better way to treat our patients and, without question, I think will be the preferred gold standard way that we take care of all of these patients in the very near future. And I pray for my patients' sake that this Panel recommends the FDA to approve this device. Thank you.

ACTING CHAIR MAISEL: Thank you. At this point, I would like to close the open public hearing

and ask the FDA and Dr. Zuckerman if they have any additional comments.

DR. ZUCKERMAN: The answer is we do, but it might be a moment.

DR. BUCKLES: While we're waiting, I'm Dave Buckles and I'm the Chief for the Peripheral Vascular Devices Branch. Do you need me to use this? Okay. I'm Dave Buckles. I'm the Chief of the Peripheral Vascular Devices Branch. On behalf of the branch, I would like to thank you for being here today. This is a valuable part of the process for us, and I have just a few brief closing comments to make on behalf of the FDA Review Team.

Okay. We're finally ready. Thank you for your patience. Next slide. I think we skipped one. Okay. Next slide. Okay. With respect to the issue of controls, I would like to put that in the context of the AAA studies that we have done, so we can leverage the experience that we have gained from the AAA stent grafts.

For the Panel-approved studies, the entire prospective controls for most studies have consisted

of concurrent controls, which were defined as patients who were not eligible for endovascular repair due to the following reasons: Inadequate neck size, inadequate access vessels and patient choice, patients who chose not to use the investigational device. I think those were some of the major issues that we talked about with respect to the controls, and these also go to the issue of whether or not we could have or should have done a randomized control trial.

For these studies, that is the AAA studies, there was general agreement that the main influence on outcomes was clamp placement, which was defined through the selection criteria in the TAG study, which we had talked about earlier. Next slide.

With respect to the major adverse events, there was quite a bit of discussion about this issue. The conclusions that we drew and that were drawn from the comparison of the major adverse event rates between the controls and the treatment groups were supported, we believe, by comparisons that we made between individual major adverse events, such as paraplegia, and given that, we believe that the data

were internally consistent. Next slide.

This is just a summation here where we talked about any major adverse event, the rates of any major adverse events, and then we matched those with, specifically, paraplegia, neurologic complications, vascular complications, wound complications and so forth. Next slide.

With respect to mortality, we believe it is most relevant for the purposes of evaluating this device to focus on aneurysm-related mortality, and in this regard there was a difference in aneurysm-related mortality favoring the TAG device out to two years. And as you saw, the mortality curves converged roughly at two years. We believe that the comparability and overall mortality rates, at that point, is related to comorbidities, which was a point that was brought out earlier in a discussion, as the deaths, at that point, were not aneurysm-related beyond the perioperative period. Next slide.

With respect to cardiac events, similarly, as for mortality, the device would not necessarily be expected to reduce cardiac events beyond the

perioperative period. Next slide.

So in summary, our assessment is that the clinical study results for the original device design were favorable. Fractures in the longitudinal spine wires in the original device were observed, but were rarely associated with clinical sequelae. Because of the observation to the fractures, the spine wires were removed and longitudinal stiffness was maintained with other device modifications. Next slide.

The 03-03 confirmatory study verified the favorable results of preclinical testing. As we discussed, there was extensive preclinical testing to compare the devices, which was followed by the confirmatory study, and the study demonstrated that device deployment was not adversely affected by the device changes. That was the purpose of the study.

And finally, importantly, all pre-specified safety and effectiveness endpoints were met for both studies. Thank you.

ACTING CHAIR MAISEL: Thank you very much. Dr. Zuckerman, do you have any additional comments from the FDA?

DR. ZUCKERMAN: No.

ACTING CHAIR MAISEL: Does the sponsor wish to make any additional comments to the Panel?

MR. NILSON: The sponsor wishes to thank everybody for their time and has no additional comments.

ACTING CHAIR MAISEL: Thank you. Mr. Morton, our industry rep, do you have any additional comments?

MR. MORTON: Thank you. Two very quick comments, one comment about expedited review, because I think the Panel will probably see more PMA expedited reviews, and it's a vehicle in which the Agency and the sponsor can agree to put a concerted effort in to try to get a needed product out to the patient population. And that's it.

ACTING CHAIR MAISEL: Thank you. Linda Mottle?

DR. FERGUSON: Can I comment on that?

ACTING CHAIR MAISEL: Yes.

DR. FERGUSON: I think if we're going to see more of these, it would be fair to the Panel to

let them know ahead of time that there may be some, how do I call them, shortcuts or whatever in whatever we get in the packet.

ACTING CHAIR MAISEL: Consider yourself warned. Our consumer rep, Linda Mottle, do you have any comments?

MS. MOTTLE: I'm okay. Thanks.

ACTING CHAIR MAISEL: Thank you. So at this point, I would like to ask Geretta to read the voting options.

EXEC. SEC. WOOD: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an Expert Advisory Panel on designated medical device pre-market approval applications, PMAs, that are filed with the Agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as "Reasonable assurance based on valid

scientific evidence that the probable benefits to health under conditions on intended use outweigh any probable risks." Effectiveness is defined as "Reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results."

Your recommendation options for the vote are as follows. Approval, if there are no conditions attached. Approvable with conditions. The Panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel. Not approvable, the Panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the vote, the Chair will ask

each Panel Member to present a brief statement outlining the reasons for their vote.

ACTING CHAIR MAISEL: So at this point, I will entertain motions for either approvable, approvable with conditions or not approvable. Dr. Johnston?

DR. JOHNSTON: I would like to move approvable with conditions.

ACTING CHAIR MAISEL: Dr. Johnston has moved approvable with conditions. Is there a second?

DR. KATO: Second.

ACTING CHAIR MAISEL: Dr. Kato has seconded the approvable with conditions. May I have a condition for the PMA?

DR. JOHNSTON: We'll discuss in detail, I assume, later and that is a post-approval study.

ACTING CHAIR MAISEL: So Condition 1 would be a post-approval study, I assume, as we had discussed earlier with --

DR. JOHNSTON: Of real-world data. I think those were your words.

ACTING CHAIR MAISEL: Can you be more

specific?

DR. JOHNSTON: 300 patients implanted after the approval of the device.

ACTING CHAIR MAISEL: With the endpoints that we discussed of paraplegia, mortality, aneurysm rupture?

DR. JOHNSTON: Correct.

ACTING CHAIR MAISEL: Okay. Do I have a second? And I also assume that would include the described post-approval follow-up of the current IDE patients as well.

DR. JOHNSTON: Correct.

DR. KATO: Excuse me. If we have to add a number in there, is 300 sufficient or does it need to be 500 or do we even talk about that number?

ACTING CHAIR MAISEL: Or we can leave it open.

DR. KATO: We don't know the number.

ACTING CHAIR MAISEL: A number adequate to detect the --

EXEC. SEC. WOOD: Dr. Johnston, would you like to revise your motion?

DR. JOHNSTON: I'm happy to.

EXEC. SEC. WOOD: Okay.

DR. EDMUNDS: Is there a discussion?

EXEC. SEC. WOOD: Yes.

ACTING CHAIR MAISEL: Yes. We are discussing a motion.

DR. EDMUNDS: Well, I would divorce the 99-01 device from the 03 device, because the 03 device is the one that is going to be followed and be marketed. And so I would like the Panel to decide how many, and I don't know that we need to do a power analysis or not. But also I would like to go out longer than five years, because I think that we should get as much information longitudinally as we possibly can from these initial cohorts.

ACTING CHAIR MAISEL: Let me put the ball back in Dr. Johnston's court, and why don't you propose your condition and we will take it from there.

DR. JOHNSTON: Shouldn't we do these one at a time?

ACTING CHAIR MAISEL: We will do a condition one at a time, and so the condition that you

have started is the post-approval study and maybe you can just describe?

DR. JOHNSTON: A post-approval study, appropriate number of patients followed for five years with the endpoints discussed previously. Is that adequate?

ACTING CHAIR MAISEL: Okay. Do I hear a second?

DR. NICHOLAS: (Seconds by hand.)

ACTING CHAIR MAISEL: Dr. Nicholas has seconded, so now we will vote on this condition for the PMA. The condition was a post-approval study with an appropriate number of patients, five-year follow-up, endpoints as we had discussed earlier, including mortality, paraplegia, aneurysm rupture, as well as the IDE studies that we had discussed earlier.

DR. BRIDGES: A point of clarification. You're not proposing a control, just device patients?

ACTING CHAIR MAISEL: Correct.

DR. BRIDGES: Okay.

ACTING CHAIR MAISEL: So we now vote on this.

DR. EDMUNDS: I have to vote against it, because it's only five years.

ACTING CHAIR MAISEL: Okay. Let's go in order here. We'll start with Dr. Yancy or can we do a show of hands, Geretta?

EXEC. SEC. WOOD: No.

ACTING CHAIR MAISEL: We have to --

EXEC. SEC. WOOD: Yes.

ACTING CHAIR MAISEL: So Dr. Yancy, for or against?

DR. YANCY: Against.

ACTING CHAIR MAISEL: Dr. Weinberger?

DR. WEINBERGER: For.

ACTING CHAIR MAISEL: Dr. Johnston?

DR. JOHNSTON: It's a part of my own motion.

ACTING CHAIR MAISEL: Dr. Normand?

DR. NORMAND: I'm confused, because I don't agree with -- I'm not supporting approval, so do I have to still vote on this?

ACTING CHAIR MAISEL: You have to vote on the approval with condition. You can vote for or

against or abstain.

DR. NORMAND: Against, I guess.

ACTING CHAIR MAISEL: Dr. Kato?

DR. KATO: For.

ACTING CHAIR MAISEL: Dr. Bridges?

DR. BRIDGES: For.

ACTING CHAIR MAISEL: Dr. Nicholas?

DR. NICHOLAS: For.

ACTING CHAIR MAISEL: Dr. Krucoff?

DR. KRUCOFF: Abstain.

ACTING CHAIR MAISEL: Dr. Lindenfeld?

DR. LINDENFELD: I'm going to vote for.

ACTING CHAIR MAISEL: Dr. Ferguson?

DR. FERGUSON: For.

DR. EDMUNDS: It's moot, but I would like it longer.

ACTING CHAIR MAISEL: Is that a for or against?

DR. EDMUNDS: It's for, but I think it's a mistake.

ACTING CHAIR MAISEL: So that motion passes 8-2-1.

DR. YANCY: Maybe this is a formality, just a point of information. We started with a motion for either approve, approvable with conditions or do not approve and we have gone immediately into amendments on that.

ACTING CHAIR MAISEL: We will vote on --

DR. YANCY: Help me with this.

ACTING CHAIR MAISEL: This is the motion, so we'll add all the conditions and then we will have a vote and if it does not pass, then we will start back at square one.

EXEC. SEC. WOOD: Let me add to that clarification. We can't vote on a motion until we know what the conditions are. If you vote for the conditions without knowing what they are, you really don't know if you support the motion or not. So we have the motion on the floor for approvable with conditions. We can't vote on that until we know what the conditions are, so we take one condition at a time. Is everybody clear on that?

ACTING CHAIR MAISEL: Are there additional conditions?

DR. FERGUSON: Well, there's the issue of the training, I think, that needs to be clarified in the conditions. I wouldn't begin to know how to verbalize that.

ACTING CHAIR MAISEL: Feel free to try.

DR. EDMUNDS: I thought that was going to be adjudicated by the FDA working with the company.

ACTING CHAIR MAISEL: So they have proposed training. The upshot of our discussion, my sense was that we did not have major additional comments regarding --

DR. LINDENFELD: I think the training proposed for people with endovascular experience is proper. I don't think we can comment on what will be proposed for those without that, but it needs to be more extensive on what is proposed. We just I don't think can comment on that at the moment.

ACTING CHAIR MAISEL: So would someone like to phrase a condition?

DR. FERGUSON: Well, I would feel comfortable with phrasing it like somebody suggested, and that is that that be worked out between the FDA

and the sponsor. I know they will do a good job of it.

ACTING CHAIR MAISEL: So appropriate training addressing all the Panel's previously mentioned concerns.

DR. FERGUSON: Yes, that would be nice.

ACTING CHAIR MAISEL: All those in favor of this? Oh, we need a second first, please. Anyone?

DR. BRIDGES: Second.

ACTING CHAIR MAISEL: Dr. Bridges has seconded. Now, we will vote for this condition. Dr. Yancy?

DR. YANCY: Against.

ACTING CHAIR MAISEL: Dr. Weinberger?

DR. WEINBERGER: For.

DR. JOHNSTON: For.

DR. NORMAND: For.

DR. KATO: For.

ACTING CHAIR MAISEL: Dr. Bridges?

DR. BRIDGES: For.

DR. NICHOLAS: For.

DR. KRUCOFF: Abstain.

DR. LINDENFELD: For.

DR. FERGUSON: For.

DR. EDMUNDS: For.

ACTING CHAIR MAISEL: Okay. So 10-0-1. Is there an additional condition? We had discussed the labeling. Dr. Kato?

DR. KATO: Yes. I would like to propose that the labeling include criteria stated on pages 38 to 44 regarding inclusion and exclusion criteria, as well as anatomic criteria as utilized in the ongoing studies.

ACTING CHAIR MAISEL: I'm sorry?

UNIDENTIFIED SPEAKER: Insert that section of labeling?

ACTING CHAIR MAISEL: So that additional data or comments you were talking about would go on which part of the labeling, the Indications For Use Statement? Is that what you're referring to, adding those things to the Indications for Use Statement?

DR. KATO: Yes.

ACTING CHAIR MAISEL: Okay. Do we have a second?

DR. FERGUSON: Second.

ACTING CHAIR MAISEL: Dr. Ferguson has seconded. We will now vote on this. We will start at the other end this time. Dr. Edmunds?

DR. EDMUNDS: For.

DR. FERGUSON: For.

DR. LINDENFELD: For.

DR. KRUCOFF: Abstain.

DR. NICHOLAS: For.

DR. BRIDGES: For.

DR. KATO: For.

DR. NORMAND: For.

DR. JOHNSTON: For.

DR. WEINBERGER: For.

DR. YANCY: Against.

ACTING CHAIR MAISEL: So we have 9-1-1. Any other conditions for this? So at this point, we can vote on this motion for approval of the PMA with conditions. Condition 1 is a post-approval study with an appropriate number of patients, five-years follow-up, power to look at endpoints of mortality, aneurysm rupture, paraplegia, not limited to those things, but

those things.

Number 2 is appropriate training addressing the aforementioned issues, and Number 3 are adding the specific inclusion/exclusion criteria from the studies that are in the packet on pages 38 to 44, specifically mentioning anatomic criteria.

That is the motion on the table. We will now vote for or against and we will start with Dr. Yancy.

DR. YANCY: Against.

ACTING CHAIR MAISEL: Dr. Weinberger?

DR. WEINBERGER: For.

ACTING CHAIR MAISEL: Dr. Johnston?

DR. JOHNSTON: For.

ACTING CHAIR MAISEL: Dr. Normand?

DR. NORMAND: Against.

ACTING CHAIR MAISEL: Dr. Kato?

DR. KATO: For.

ACTING CHAIR MAISEL: Dr. Bridges?

DR. BRIDGES: For.

ACTING CHAIR MAISEL: Dr. Nicholas?

DR. NICHOLAS: For.

ACTING CHAIR MAISEL: Dr. Krucoff?

DR. KRUCOFF: Abstain.

ACTING CHAIR MAISEL: Dr. Lindenfeld?

DR. LINDENFELD: For.

ACTING CHAIR MAISEL: Dr. Ferguson?

DR. FERGUSON: For.

ACTING CHAIR MAISEL: Dr. Edmunds?

DR. EDMUNDS: For.

ACTING CHAIR MAISEL: So that motion passes. We have 8-2-1. We'll now go around the table and comment on why you voted the way you did. Dr. Yancy?

DR. YANCY: The first thing I would like to do is to applaud the company and the investigators for making a concerted effort to bring forward new technology. I think that is very important. And I am especially, as a clinician, very sensitive to the very impassioned pleas from the practitioners in the audience. But I believe that we have to, at some point in time, no longer dismiss science in the process of looking at devices. And we are voting to move forward with a platform that has been cited in a

few number of patients with sufficient ambiguities that we have attached a number of provisos to the amendment that really speak for the need for a lot more information.

And so in my judgment, I think it's technology that needs to be pursued. I would love to see it in the marketplace, but in response to the question how could we not do this, my response is how can we do this with such thin data and is it ethical to move forward with a platform where we really don't have that kind of definitive information?

So I trust that we will be due diligent with the provisos, particularly the post-marketing survey. I really think we lose the leverage to get information once something is approved, but perhaps this will be the ground breaking initiative where we will get good quality data despite approval.

ACTING CHAIR MAISEL: Dr. Weinberger?

DR. WEINBERGER: I think that it's very clear that there were many problems with this PMA application. So notwithstanding the fact that I would like to congratulate everyone involved, I know this

was hard to do. This study did not have adequately executed control groups, which we have spoken about in detail. I think the complexity of the endpoint made interpretation very difficult for us.

Nevertheless, what is very obvious, without too much extrapolation, is that this is a far less morbid procedure than what is currently available surgically. We would like data that proves that there is a mortality benefit, but under the circumstances and having lived through taking care of patients with this disease, I don't think that I'm in a position to try to withhold a therapy that will very clearly decrease the morbidity of the procedure to such an obvious extent.

So for that reason, I voted for, although I will agree with Dr. Yancy that the scientific evidence is somewhat thin and the execution of the clinical trial could certainly have been buffed up a bit.

ACTING CHAIR MAISEL: Dr. Johnston?

DR. JOHNSTON: I did not enjoy reading the data in detail. I found it challenging, but having

said that, I believe the company should be congratulated fully on recognizing a problem with the prosthesis, for fixing it and, in the process of doing that, for developing what I perceive as some very new and novel testing techniques that I'm sure the FDA is going to find extremely useful in the future.

When it comes to making a decision, I, too, was concerned about the comparative group and in my questioning tried to address the major morbidity that was associated. I did conclude that the morbidity, in fact, was lower than a comparative group, the comparative one they presented and the comparative groups that one would find in the literature or from our own experience, and also that the aneurysm mortality was lower and it was for those reasons that I supported it.

ACTING CHAIR MAISEL: Dr. Normand?

DR. NORMAND: I didn't support this device for reasons that have already been iterated. I don't think there was scientific evidence to support it and I don't want to do things on intuition and hope, and so that's why I voted against it.

ACTING CHAIR MAISEL: Dr. Kato?

DR. KATO: While I must agree with many of my colleagues that the studies presented, at least in the control group, were probably nothing short of atrocious. I am hopeful that the conditions, and specifically the very detailed labeling conditions, which this Panel recommended today, will be added, because it is my belief that I do think that this is a novel technology, which looks like it should work. And before it is released to the public with a very minimal label that we should continue on with, basically, an ongoing study with very tight labeling conditions and with follow-up provided by the sponsor, which provides granular data, so that we can come back and reassess this in another few years.

ACTING CHAIR MAISEL: Dr. Bridges?

DR. BRIDGES: I voted in favor of the device, because, I mean, I certainly understand the concerns with respect to the control group and the lack of comparability, and I think that there is more that could have been done from a statistical point of view to try to assure that the two groups were

comparable to a greater degree. So I mean, I think that a better job could have been done there.

However, I think it's clear that the device is beneficial and I think it's clear that there is less complications in general associated with implantation of this device under the indications and exclusions for which it has been applied, because we certainly know that other devices, when applied outside the inclusion and exclusion criteria, will often have inferior results. And so I think Dr. Kato's added condition is an important one and given that, I feel confident that the appropriate thing to do is to approve the device.

ACTING CHAIR MAISEL: Dr. Nicholas?

DR. NICHOLAS: I approved the device for several reasons. I think, first, the data clearly has concerns of flaw. I agree with everyone who has reiterated that. But I think when the day comes to the end, I have got to say, Dr. Sicard and Dr. White stated it, that a vascular surgeon who has seen both sides of the treatment of the disease has got to vote with his heart that this is clearly a step forward in

the care of our patients.

And I think I can say that safely with maybe less than ideal science today if we have this excellent post-approval study that will be very helpful in assuring us that the data, indeed, supported the judgment to move ahead with this.

ACTING CHAIR MAISEL: Mitch?

DR. KRUCOFF: Well, I abstained, because I literally can't figure out where to come down. There is clearly very compelling structural, intuitive rationale. I think the reason this is expedited is very real. This is a very severe patient problem and at many levels, as you look at what was presented today in the device itself, this is clearly a better opportunity for a patient suffering this disease than the surgical therapy or other.

The trouble is I really cannot get through a version of this that lets me feel like I have data to support that. And the frustrating thing for me is that actually, I think the information was probably around. It's just that the pieces that are missing are enough to make a difference.

So I sincerely hope that this is not an endemic indication of what expedited review is likely to bring us, which is half-baked, half-cooked. I can honestly say I was not assisted. I did not personally feel like either presentation of the data from the company or from the FDA helped me understand how to vote on this issue.

So I do appreciate the investigators. I think they make it very clear, and I think we heard many surgical voices, people who do this work through the day. We heard from patients. But we have also just completed an interventional trial where we retrieved debris from acute MI vessels in 71 percent of patients that showed no benefit at all and another one where it actually harmed patients.

So voting on intuition and voting on your heart I don't think is the process at least that I signed up to join for the Panel. So I'm stuck, because I really, honestly, at one level do believe this is a great opportunity for patients and lead edge technology and a new dawn, but at the same time I don't feel like I have the information to vote in

support of that nor do I really have the information to say I think it's wrong, so I abstained.

ACTING CHAIR MAISEL: Joanne?

DR. LINDENFELD: As everybody stated, this is a very difficult decision, and I think that we all want data and I agree with Mitch that neither presentation, I think, really got to the data that we needed to feel more comfortable approving this.

However, despite all that, when I correct back and look at the lack of an early mortality problem with the device and other signals that the device is actually worsening things, the overall benefit on hospital stay sways me to approve this. But I would hope, again I would just state what Mitch said again, is that expedited review doesn't mean this kind of relatively poor analysis of the data.

ACTING CHAIR MAISEL: Dr. Ferguson?

DR. FERGUSON: Well, I voted for, because I really think this is a giant step forward in the care of patients with aneurysms of the aorta. I spent most of my clinical career operating on these thoracic aneurysms that were presented and I have had some

successes, but I have never had a group of patients that I anguished over more, I guess, than this group. This is a definite step forward for these patients in the future and I applaud it.

ACTING CHAIR MAISEL: Dr. Edmunds?

DR. EDMUNDS: I voted for, because I think that the data presented by the company that's descriptive data for the 01 and the 03 devices, common sense trumps a demand for statistical perfection and a huge operation with considerable morbidity.

ACTING CHAIR MAISEL: Thank you very much. Do our industry rep or consumer rep have any additional comments? Seeing none, this concludes the report on recommendations of the Panel on PMA P040043 from W.L. Gore and Associates. We are adjourned.

(Whereupon, the meeting was concluded at 5:18 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Circulatory System Devices Panel

Before: DHHS/PHS/FDA/CDRH

Date: January 13, 2005

Place: Gaithersburg, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.